UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY

IN RE VALSARTAN, LOSARTAN, AND IRBESARTAN PRODUCTS LIABILITY LITIGATION	**MDL No. 2875**
THIS DOCUMENT RELATES TO ALL CASES	**HON. ROBERT B. KUGLER** **CIVIL NO. 19-2875 (RBK)**

PLAINTIFFS' BRIEF IN SUPPORT OF *DAUBERT* MOTION TO PRECLUDE DEFENSE EXPERT JASON O. CLEVENGER FROM OFFERING CLASS CERTIFICATION OPINIONS

HOLLIS LAW FIRM
8101 College Blvd, Suite 260
Overland Park, KS 66210
913-385-5400
913-385-5402 fax

On the Brief:
C. Brett Vaughn RN, BSN, JD

TABLE OF CONTENTS

I. INTRODUCTION 1

II. APPLICABLE LAW 2

III. ARGUMENT 3

A. Dr. Clevenger's Opinion that Nitrosamine Contaminated Valsartan is Equivalent to the Reference Listed Drug Per the USP Monograph Ignores the USP's Public Statement on Nitrosamine Impurities in Valsartan 3

B. Dr. Clevenger's Opinion that Aurobindo's ANDA Approval Suggests Aurobindo Conducted an Adequate Risk Assessment is Speculative and a Net Opinion 5

C. Dr. Clevenger's Opinion that NDEA Levels Decrease from Aurobindo's API to Finished Dose is Based on an Invalid Testing Methodology and Inaccurate Results, and Ignores Contrary FDA Validated Testing Results 7

IV. CONCLUSION 10

TABLE OF AUTHORITIES

Cases

Claar v. Burlington, N.R.R.,
29 F.3d 499 (9th Cir. 1994) 3

Daubert v. Merrell Dow Pharmaceuticals, Inc.,
509 U.S. 579 (1993) 2

Daubert v. Merrell Dow Pharmaceuticals, Inc.,
43 F.3d 1311 (9th Cir. 1995) 3

Elcock v. Kmart Corp.,
233 F.3d 734 (3d Cir. 2000) 3

General Elec. Co. v. Joiner,
522 U.S. 136 (1997) 3

Kumho Tire Co. v. Carmichael,
526 U.S. 137 (1999) 3

Magistrini v. One Hour Martinizing Dry Cleaning,
180 F. Supp. 2d 584 (D.N.J. 2002), *aff'd,* 68 Fed. Appx. 356 (3d Cir. 2003) 3

Padillas v. Stork-Gamco, Inc.,
186 F.3d 412 (3d Cir. 1999) 2

In re Paoli R.R. Yard PCB Litig.,
35 F.3d 717 (3d Cir. 1994) ..... *passim*

In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.,
858 F.3d 787 (3d Cir. 2017) ..... *passim*

Rules

Fed. R. Evid. 702 2

I. INTRODUCTION

Aurobindo retained Exponent, Inc. to review some of Aurobindo's "documents, testimony and analytical testing data regarding nitrosamine impurities in valsartan active pharmaceutical ingredients (API) and final drug product." (ECF 2023-8, Clevenger Report at 1-2). Dr. Jason Clevenger, with a background in cGMP and chemistry, submitted an expert report on behalf of Exponent, Inc. Dr. Clevenger offers pharmaceutical equivalency opinions (which he incorrectly conflates with bioavailability and bioequivalence) to rebut Plaintiffs' expert Dr. Kali Panagos and Dr. Ron Najafi. (ECF 2023-8, Clevenger Report at 6-10). Additionally, Dr. Clevenger opines that the nitrosamine levels in Aurobindo's finished drug product is less than is present in its corresponding API. (ECF 2023-8, Clevenger Report at 10-14).

Dr. Clevenger bases his bioequivalency opinion on the fact that the US Pharmacopeia's (USP) valsartan monograph does not specifically state that valsartan should be tested for nitrosamine impurities. Dr. Clevenger agreed that the USP monograph for valsartan doesn't list impurities with no acceptable limit, but Dr. Clevenger never reviewed the USP's website, which states that nitrosamines are unacceptable impurities in valsartan containing drugs. Similarly, Dr. Clevenger ignored (because he was not given) large swaths of FDA and Aurobindo testing data that does not support his opinion that the level of nitrosamines in Aurobindo's finished drug product is less than is present in its corresponding API. His opinions are thus net opinions as discussed below.

Dr. Clevenger was only given select favorable or ambiguous documents by the defense to review in forming his opinions, while documents that would undermine Dr. Clevenger's opinions were withheld from him. Therefore, Dr. Clevenger's opinions should be excluded for being unreliable, as he did not consider contrary evidence.

II. APPLICABLE LAW

The admissibility of expert testimony is determined pursuant to Federal Rule of Evidence 702. "As a gatekeeper, courts are supposed to ensure that the testimony given to the jury is **reliable** and will be more informative than confusing." *In re Zoloft (Sertraline Hydrochloride) Prods. Liab. Litig.*, 858 F.3d 787, 800 (3d Cir. 2017). Additionally, "[b]oth an expert's methodology and the application of that methodology must be reviewed for reliability." *Id.* at 791. The "specific way an expert conducts such an analysis must be reliable; '**all of the relevant evidence must be gathered**, and the assessment or weighing of that evidence must not be arbitrary, but must itself be based on methods of [the relevant field].'" *Id.* at 796.

This Court recently applied these principles in ruling on the *Daubert* motions filed in connection with the parties' general causation experts. The party offering the proposed expert testimony bears the burden of establishing the admissibility of the testimony by a preponderance of the evidence. *Padillas v. Stork-Gamco, Inc.,* 186 F.3d 412, 417-18 (3d Cir. 1999). An "expert's opinions must be based on the methods and procedures of [the relevant field], rather than on subjective belief or unsupported speculation." *In re Paoli R.R. Yard PCB Litig.*, 35 F.3d 717, 742 (3d Cir. 1994) (citations and internal quotations omitted). Thus, "the expert must have 'good grounds' for his or her belief." *Id.* (quoting *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 590 (1993)). These good grounds must support each step of the analysis and, "*any* step that renders the analysis unreliable under the *Daubert* factors renders the expert's testimony inadmissible." *Id.* at 745. A court should also consider the methodology's error rate when assessing its reliability. *Paoli*, 35 F.3d at 742 n.8. Judges within this Circuit also consider how and when the methodology is used outside of litigation. *Id.* at 742 (discussing reliability factors under *Daubert* and Third Circuit case law).

Furthermore, "*Daubert*'s gatekeeping requirement .... make[s] certain that an expert, whether basing testimony upon professional studies or personal experience, employs in the courtroom the same level of intellectual rigor that characterizes the practice of an expert in the relevant field.'" *Elcock v. Kmart Corp.*, 233 F.3d 734, 746 (3d Cir. 2000) (quoting *Kumho Tire Co. v. Carmichael*, 526 U.S. 137, 152 (1999)); *see also Magistrini v. One Hour Martinizing Dry Cleaning*, 180 F. Supp. 2d 584, 594 (D.N.J. 2002*), aff'd,* 68 Fed. Appx. 356 (3d Cir. 2003). In addition, the following factors are relevant when determining reliability:

> (i) whether the expert's proposed testimony grows naturally and directly out of research the expert has conducted independent of the litigation (*see Daubert v. Merrell Dow Pharmaceuticals, Inc.,* 43 F.3d 1311, 1317 (9th Cir. 1995)); (ii) whether the expert has unjustifiably extrapolated from an accepted premise to an unfounded conclusion (*see General Elec. Co. v. Joiner,* 522 U.S. 136, 146, 118 S.Ct. 512, 139 L.Ed.2d 508 (1997)); (iii) whether the expert has adequately accounted for alternative explanations (*see Claar v. Burlington, N.R.R.,* 29 F.3d 499 (9th Cir. 1994)).

Magistrini, 180 F. Supp. 2d at 594–95. To this end, the Third Circuit has recently affirmed the exclusion of expert testimony that "failed to consistently apply the … methods … articulate[d], … deviated from or downplayed certain well-established principles of [the] field, and … inconsistently applied methods and standards to the data so as to support [an] a priori opinion." *Zoloft*, 858 F.3d at 792.

III. ARGUMENT

A. Dr. Clevenger's Opinion that Nitrosamine Contaminated Valsartan is Equivalent to the Reference Listed Drug Per the USP Monograph Ignores the USP's Public Statement on Nitrosamine Impurities in Valsartan

In his expert report, Dr. Clevenger makes the unsupported and illogical leap that just because the USP monograph doesn't specifically state that valsartan should be tested for

nitrosamines, that nitrosamine contaminated valsartan is considered pharmaceutically equivalent to the reference listed drug ("RLD"):

> As none of the valsartan monographs specifically direct that the material should be tested for nitrosamine impurities, the valsartan batches at issue met the identical compendial standard, i.e., the USP monograph, of "identity, strength, qualify, and purity" to be considered pharmaceutically equivalent to the reference listed drug.

(ECF 2023-8, Clevenger Report at 8). However, when asked if the USP list impurities that have no acceptable limit, Dr. Clevenger conceded, "[n]ot in that monograph for valsartan." (ECF 2023-7, Clevenger 3/18/22 Depo Tr. 76:14-17). While the USP monograph itself doesn't specifically direct companies to test their valsartan for nitrosamines, the USP website on nitrosamine impurities in angiotensin II receptor blockers (ARBs) notes that "[c]ompanies are responsible for understanding their manufacturing processes, which includes identifying and preventing the presence of ***unacceptable impurities***" and that the "USP is supporting manufacturers and regulators with tools and solutions for testing, assessing risk and understanding potential sources related to nitrosamine impurities." (ECF 2023-6, USP Nitrosamine Impurities Webpage (emphasis added)). Thus, there has always been a requirement to prevent "unacceptable impurities" built into the USP description of valsartan's specifications. Mutagenic impurities that are not listed in the specifications have never been acceptable based on the failure by the specifications to state the obvious, which is that they were prohibited unless some specification was provided allowing up to a certain amount. When confronted with the USP's webpage and asked if the USP was in fact describing nitrosamines as unacceptable impurities in valsartan, Dr. Clevenger answered, "**I think there are - - I mean, the statement - - the statement certainly appears to reflect USP's position**." (ECF 2023-7, Clevenger Depo Tr. 78:3-25 (emphasis added)). Dr. Clevenger then conceded that he had not seen the USP's webpage on nitrosamine impurities in ARBs prior to his deposition. (ECF 2023-7, Clevenger Depo Tr. 79:14-21). Thus, Dr. Clevenger conceded that the

USP prohibited NDMA and NDEA in valsartan once confronted with the documents he had not reviewed prior to his deposition.

Finally, Dr. Clevenger admitted that not only does the USP monograph apply to contamination, but so do cGMP practices:

> A: Looks, with respect to the USP monograph, that's one component of it. There are - - the aspect of cross-contamination is **also dealt with the in GMP world, and I would think that that's where your hypothetical example is leading and would be dealt with**.
>
> Q: So cGMP practices should prevent these types of contaminations, correct?
>
> A: That's the area where it would be dealt with.

(ECF 2023-7, Clevenger Depo Tr. 73:9-22 (emphasis added)).

Dr. Clevenger should be precluded from offering the net opinion that because the USP monograph does not specifically direct that valsartan be tested for nitrosamine impurities, that valsartan contaminated with nitrosamines are pharmaceutically equivalent to the RLD, because he did not review all relevant evidence. *Zoloft*, 858 F.3d at 796. Moreover, once shown the information he had not seen, he conceded the opposite – that the presence of NDEA and NDMA constituted a violation of the USP standard.

B. Dr. Clevenger's Opinion that Aurobindo's ANDA Approval Suggests Aurobindo Conducted an Adequate Risk Assessment is Speculative and a Net Opinion

Dr. Clevenger speculates in his report that because Aurobindo was required to conduct a risk assessment as part of its original ANDA and that because the FDA approved Aurobindo's ANDA, it "***suggests*** that [Aurobindo's] initial risk assessment met the requirements without specifically testing for nitrosamine impurities." (ECF 2023-8, Clevenger Report at 9-10 (emphasis added)). Not only is this an improper and unhelpful regulatory net opinion, but it also neglects the fact that Aurobindo's risk assessment never identified that nitrosamines could form from its valsartan manufacturing process. To be clear, the risk assessment must identify the potential

formation of impurities, and then the process validation must be set up to test for the potential impurities to ensure they do not exist, or if they do at what level. From there, determinations can be made as to whether remedial action is required and/or the specifications can be accurately set to provide for allowable levels and testing to ensure those levels (if any is permitted) will not be exceeded. Aurobindo's failed risk assessment led to the absence of testing for nitrosamines and the absence of any specifications addressing nitrosamines. (Ex. A, Singh 5/21/21 Depo Tr. 821:15-822:5).

Dr. Clevenger attempted to bolster his opinion by citing to Aurobindo's post-recall root cause investigation that concluded "there is no possibility of formation of Nitrosamine impurities (NDMA or NDEA) in the process." (ECF 2023-8, Clevenger Report at 10). However, this was precisely the problem with Aurobindo's initial risk assessment—it failed to properly assess the possibility of nitrosamines forming in its valsartan process, which was confirmed by the regulatory consulting firm Aurobindo employed in relation to the valsartan nitrosamine contamination:

> Previously the manufacturing process was assessed, and it was concluded there was no possibility of NDMA or NDEA being formed. **This was found to be incorrect, as only the reaction was being considered, not sources of impurities in the materials that could participate in the reaction.**

(Ex. B, APL-MDL-2875-0251669 at 1793; ECF 2023-7, Clevenger Depo Tr. 208:5-210:14). Thus, his opinion relying on the accuracy of the risk assessment is rested on a false foundation/flawed hypothetical and thus constitutes a net opinion. When asked if he concluded in his expert report that there was no possibility of nitrosamines being formed, Dr. Clevenger answered, [redacted]" (ECF 2023-7, Clevenger Depo Tr. 210:4-14). That statement proves nothing other than the failure by the expert to take into account significant parts of the record that proved his

assumption was false. Dr. Clevenger's opinion is unsupported by the factual record, rendering it a net opinion. *See Paoli*, 35 F.3d at 742, 745.

C. Dr. Clevenger's Opinion that NDEA Levels Decrease from Aurobindo's API to Finished Dose is Based on an Invalid Testing Methodology and Inaccurate Results, and Ignores Contrary FDA Validated Testing Results

Exponent also reviewed a spreadsheet containing some of Aurobindo's internal testing of the NDEA and NDMA levels in batches of its VCDs and API in coming to the opinion that "elevated temperatures used during manufacturing of Aurobindo's valsartan-containing drug product likely resulted in volatilization of nitrosamine impurities present in certain batches of the active pharmaceutical ingredient (API), resulting in generally lower levels of impurities in the finished drug product batches than the corresponding API batches used to manufacture the drug product."[1] (ECF 2023-8, Clevenger Report at 10, 12). However, Dr. Clevenger just "[redacted]" and did nothing to confirm Aurobindo's methodology prior to submitting his expert report. (ECF 2023-7, Clevenger Depo Tr. 34:3-17). Dr. Clevenger had requested that defense counsel provide him with [redacted]. (ECF 2023-7, Clevenger Depo Tr 87:1-24). Additionally, Defendant [redacted], which Dr. Clevenger solely based his opinions on. Specifically, Dr. Clevenger was [redacted]. (ECF 2023-7, Clevenger Depo Tr. 129:10-15,

[1] Aurobindo's regulatory consultant noted that opinions such as this "[redacted]" (Ex. C, APL-MDL-2875-0048766 at 767; ECF 2023-7, Clevenger Depo Tr. 239:3-241:16).

139:10-13, 142:21-143:1, 161:12-16, 180:9-181:22, 213:11-25, 242:5-8, 250:16-22, 259:12-20, 268:6-270:11).

Upon being shown that Aurobindo's initial internal results frequently detected [redacted]. (ECF 2023-7, Clevenger Depo Tr. 129:10-138:13; Ex. D, APL-MDL-2875-0102832 at 835[2]). Dr. Clevenger then conceded that he had "[redacted]" (ECF 2023-7, Clevenger Depo Tr. 138:19-20), and that the FDA does not explicitly list Aurobindo's testing method as an appropriate way to test VCDs for nitrosamines. (ECF 2023-7, Clevenger Depo Tr. 119:1-4).

Dr. Clevenger was then shown for the first time the [redacted]. (ECF 2023-7, Clevenger Depo Tr. 142:21-143:1; Ex. D, APL-MDL-2875-0102832 at 859-860). Upon reviewing all the data, Dr. Clevenger agreed that [redacted], which are what he relied on. (ECF 2023-7, Clevenger Depo Tr. 143:15-22, 144:12-16).[3] Aurobindo's regulatory consultant noted that "[t]he Aurobindo testing method has poor reproducibility" and that "[i]n-house results are consistently much lower than FDA results." (Ex. E, APL-MDL-2875-0135474 at 477-478). Additionally, Dr. Clevenger did not review the [redacted], which would have revealed that the pills Aurobindo initially tested were sent in a [redacted], while the pills Aurobindo retested were

[2] The FDA detected [redacted].

[3] Of note, while Aurobindo's retest results actually detected NDEA in their VCDs that their initial testing did not, Aurobindo's retest results were still significantly lower than the FDA's results on the same batches (.270 ppm v .128 ppm; .120 ppm v .070 ppm; .590 ppm v .097 ppm).

sent in a [redacted]. (Ex. F, APL-MDL-2875-0076155 at 173; ECF 2023-7, Clevenger Depo Tr. 184:15-188:6). Aurobindo concluded that "[redacted]." (Ex. F, APL-MDL-2875-0076155 at 173). Dr. Clevenger relied only on Aurobindo's initial testing results, which are inconsistent with the FDA's testing results and Aurobindo's retesting results, and Aurobindo cannot even verify that they tested the correct samples the first time around.[4] The very foundation of Dr. Clevenger's opinion is based on unreliable, carefully selected data, and not in conformance to any acceptable methodology.

Dr. Clevenger also did not recall comparing the FDA's results for Aurobindo's VCDs with Aurobindo's results for the corresponding batches of API. (ECF 2023-7, Clevenger Depo Tr. 120:8-12, 147:20-23; Ex. D, APL-MDL-2875-0102832 at 860-861). After matching up Aurobindo's API testing results with the FDA's corresponding finished dose testing, Dr. Clevenger repeatedly agreed that Aurobindo's API testing results were [redacted]. (ECF 2023-7, Clevenger Depo Tr. 150:12-17, 151:16-23, 152:12-17, 153:15-21, 154:10-15). Importantly, Dr. Clevenger agreed that the levels of NDEA in batches of Aurobindo's API were [redacted]. (ECF 2023-7, Clevenger Depo Tr. 149:13-150:10, 151:11-14, 152:2-11, 152:22-153:14). Thus, contrary to Dr. Clevenger's opinion, the NDEA levels in Aurobindo's API didn't decrease when compared to the FDA's validated testing of Aurobindo's VCDs.

[4] Aurobindo released VCD's onto the market based on their initial testing, which Aurobindo's regulatory consultant compared to the FDA's testing results and noted [redacted] (Ex. C, APL-MDL-2875-0048766 at 768).

Dr. Clevenger's opinion that the amounts of NDEA in Aurobindo's finished dose products is less than the amount of NDEA in corresponding batches of API is only supported by Aurobindo's inaccurate, unreliable, and unvalidated initial testing methodology. At the same time, Dr. Clevenger ignores FDA validated testing results that contradict his opinion. As such, Dr. Clevenger's opinions related to the levels of NDEA in Aurobindo's VCDs are unreliable and should be precluded. *Zoloft*, 858 F.3d 787.

IV. CONCLUSION

For the foregoing reasons, Dr. Clevenger should be excluded from offering his opinions.

Dated: May 3, 2022

Respectfully submitted,

By: /s/ C. Brett Vaughn
C. Brett Vaughn RN, BSN, JD
Hollis Law Firm
8101 College Blvd, Suite 260
Overland Park, KS 66210
Phone: 913-385-5400
Fax: 913-385-5402
Email: Brett@HollisLawFirm.com